KAPLAN MEDICAL

# Pharmacodynamics and Pharmacokinetics

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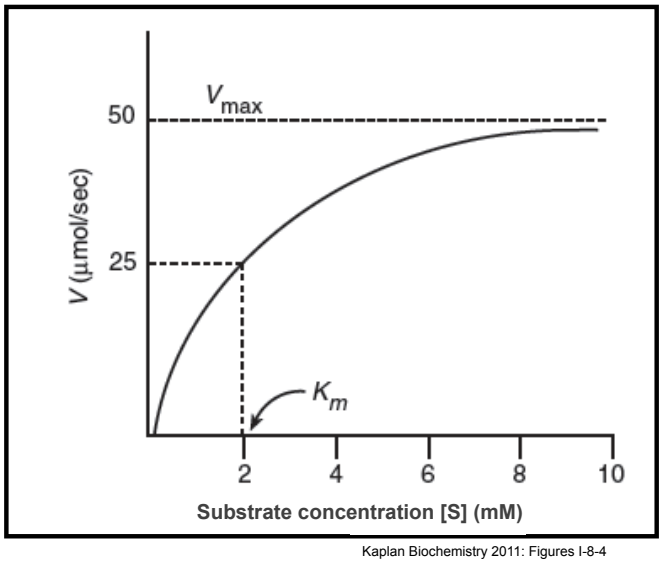
## Enzyme kinetics

**$V_{max}$ =** maximum reaction velocity for a given amount of enzyme

- Proportional to enzyme concentration

**Michaelis-Menten plot**




Kaplan Biochemistry 2011: Figures I-8-4

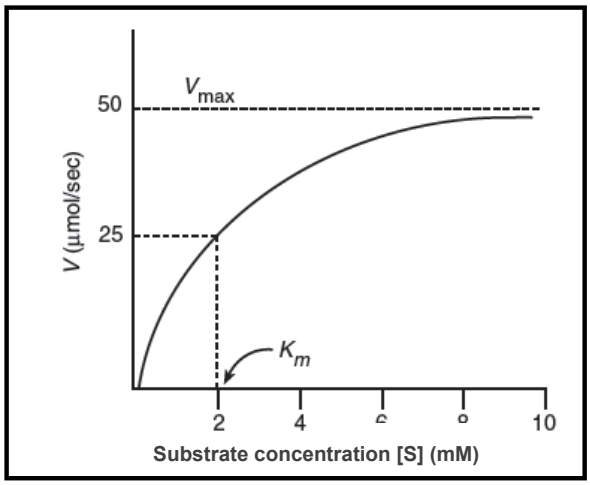
FA 2012: 258.1 • FA 2011: 232.1 • FA 2010: 228
ME 3e: 55

# Enzyme kinetics

**Michaelis constant ($K_m$):** Substrate concentration required to reach half $V_{max}$ = $1/\text{affinity}$

- High $K_m$ → low affinity
- Low $K_m$ → high affinity

**Michaelis-Menten plot**




Kaplan Biochemistry 2011: Figures I-8-4

FA 2012: 258.1 • FA 2011: 232.1 • FA 2010: 228
ME 3e: 55

x1.5 PH01-3

# Enzyme kinetics

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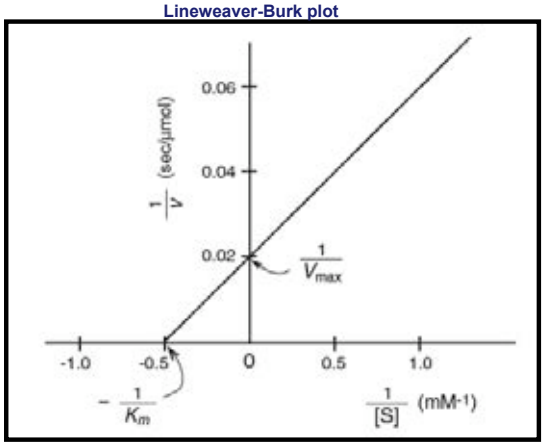
**$V_{max}$ =** maximum reaction velocity for a given amount of enzyme

- Proportional to enzyme concentration

**Lineweaver-Burk plot**




Kaplan Biochemistry 2011: Figure: I-8-5

FA 2012: 258.1 • FA 2011: 232.1 • FA 2010: 228
ME 3e: 55

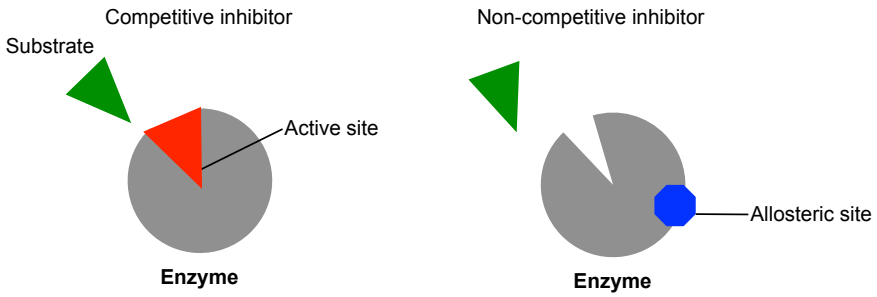
# Enzyme inhibitors

## Competitive inhibitors

- Resemble substrate, bind at active site
- Increasing substrate concentration can overcome inhibition
- Decrease *potency*

## Non-competitive inhibitors

- Typically bind at allosteric site, not near active site
- Cannot be overcome with increased substrate concentration
- Decrease *efficacy*



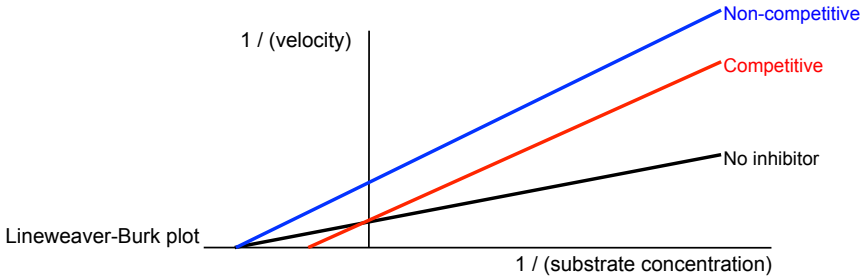

FA 2012: 258.1 • FA 2011: 232.1 • FA 2010: 228
ME 3e: 55

x1.5 PH01- 5

# Enzyme inhibitors

Competitive vs. Non-competitive inhibitors

| | Competitive | Non-competitive |
|---|---|---|
| Resemble substrate | Yes | No |
| Overcome with ↑substrate concentration | Yes | No |
| Bind active site | Yes | No |
| $V_{max}$ | No effect | ↓ |
| $K_m$ | ↑ | No effect |
| Pharmacodynamics | ↓Potency | ↓Efficacy |
| Graphs cross? | Yes | No |




FA 2012: 258.1 • FA 2011: 232.1 • FA 2010: 228
ME 3e: 55

x1.5 PH01- 6

# Volume of distribution

$$\text{Volume of distribution, } \mathbf{V_d} = \frac{\text{total amount of drug in body}}{[\text{drug}]_{plasma}} \quad (\textit{liters})$$

| | |
|---|---|
| **Low $V_d$ (4-8 L)** | mostly in blood |
| **Mid $V_d$ (12-14 L)** | mostly extracellular fluid |
| **High $V_d$ (>total body water)** | distributed in all tissues, non-fluid compartments (fat) |

$V_d$ of plasma protein bound drugs are altered in liver and kidney disease

- Hepatic disease: ↓ synthesis of plasma proteins
- Renal diseases: Plasma proteins (and bound drugs) are excreted in the urine

FA 2012: 259.1 • FA 2011: 232.2 • FA 2010: 228
ME 3e: 166

x1.5 PH01-7

# Drug clearance

$$\textbf{Clearance (Cl)} = \frac{\text{Rate of drug elimination}}{\text{Plasma drug concentration}} = V_d \times k_e$$

- Clearance refers to the volume of blood totally cleared of drug per unit time
- Units:
  - Rate of drug elimination: (mass)/(units of time)
  - Plasma drug concentration: (mass)/(volume of plasma)
  - Elimination rate constant ($k_e$): $t^{-1}$
- Renal clearance:
  - Clearance:
    - Equals **glomerular filtration rate (GFR)** when there is no reabsorption, secretion, or plasma protein binding
    - Inulin and creatinine clearance are used to estimate GFR
  - Protein-bound drugs are not cleared
    - Clearance = (free fraction) x GFR

FA 2012: 259.1 • FA 2011: 232.2 • FA 2010: 228
ME 3e: 166

x1.5 PH01-8

# Drug half-life

- Amount of time it takes for an amount of drug in the body to change by one half

$$t_{1/2} = \frac{0.7 \times V_d}{\text{Clearance}}$$

- Half-life relates to both a decrease in plasma concentration via elimination or an increase in plasma concentration via drug infusion
- Steady state is reached in 4-5 half-lives with continuous infusion

| n $t_{1/2}$ [drug] | 1 $t_{1/2}$ | 2 $t_{1/2}$ | 3 $t_{1/2}$ | 4 $t_{1/2}$ | 5 $t_{1/2}$ |
|---|---|---|---|---|---|
| | 50 % | 75 % | 87.5 % | 93.75 % | 96.9 % |

FA 2012: 259.1 • FA 2011: 232.2 • FA 2010: 228
ME 3e: 166

x1.5 PH01- 9

# Loading and maintenance doses

## Loading dose

- Large initial dose given to fill up $V_d$
- Can increase plasma concentration in less than 4-5 half-lives

$$LD = \frac{V_d \times C_p}{F}$$

$C_p$ blood plasma conc.
Cl clearance
F bioavailability

## Maintenance dose

- Given to maintain constant blood plasma levels
- Lowered if hepatic/renal function is impaired

$$MD = \frac{Cl \times C_p}{F}$$

## Bioavailability (F) F = 1 for IV infusion

- Fraction of administered drug that reaches systemic circulation
- Some drugs fail to be absorbed, or are metabolized before reaching circulation

FA 2012: 259.2 • FA 2011: 233.1 • FA 2010: 229
ME 3e: 167

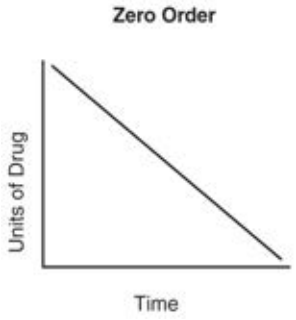
x1.5 PH01- 10

# Drug elimination

## Zero order elimination

- Constant **amount** of drug eliminated with time
- Phenytoin, aspirin, ethanol

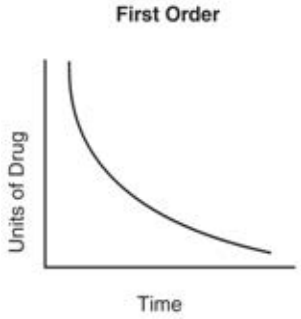
100 mg → 90 mg → 80 mg → 70 mg → …




## First order elimination

- Constant **fraction** of drug eliminated with time
- Most drugs follow first-order kinetics

100 mg → 50 mg → 25 mg → 12.5 mg → …

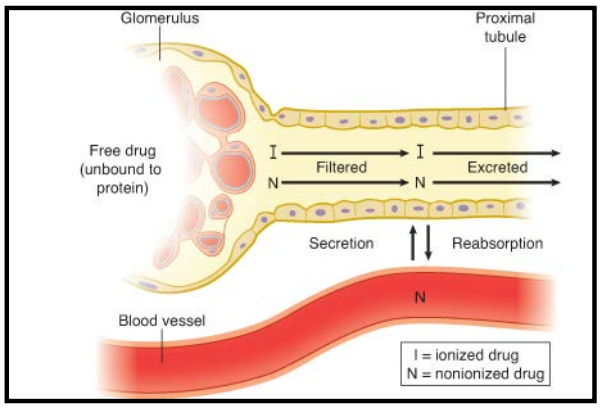



FA 2012: 260.1 • FA 2011: 233.2 • FA 2010: 229
ME 3e: 166

x1.5 PH01- 11

# Renal excretion

- Both ionized (I) and nonionized (N) forms are filtered
- Only non-ionized forms are actively secreted or reabsorbed
- Ionized forms of drug are "trapped" in filtrate
- Drugs that are weak acids:
  - Barbiturates, methotrexate, aspirin,
- Drugs that are weak bases:
  - Amphetamines




Kaplan Pharmacology 2011: Figure I-1-3

| | | | |
|---|---|---|---|
| Alkalinization of urine [$(HCO_3^-)$ + Weak Acid]: | R–COOH (crosses membranes) | ⇌ | $R–COO^- + H^+$ (better cleared) |
| Acidification of urine [$(NH_4Cl)$+Weak Base] | $R–NH_2 + H^+$ (crosses membranes) | ⇌ | $R–NH_3^+$ (better cleared) |

FA 2012: 260.2 • FA 2011: 233.3 • FA 2010: 229
ME 3e: 166

x1.5 PH01- 12

# Biotransformation

•Occurs in the liver

•Conversion of lipid soluble drugs into water soluble metabolites → ↑ renal excretion

•Two forms of drug metabolism: Phase 1 and 2

**Phase I:**

•Three mechanisms of metabolization: Oxydation, reduction, and hydrolysis

• Cytochrome P450 enzymes:

- Located in smooth endoplasmic reticulum of the liver (to lesser extent GI, lungs, kidneys
- Require O2 and NADP
- Mechanisms of cytochrome P450 enzyme metabolism:
  - Reduction
  - Oxidation
    - Hydroxylation and dealkylation

FA 2012 260 • FA 2011: 233.4 • FA 2010: 229.4
ME 3e: 167



# Cytochrome P-450 interactions

| Inducers | Inhibitors |
|---|---|
| Quinidine | HIV protease inhibitors |
| Barbiturates | Isoniazid (INH) |
| St. John's wort | Sulfonamides |
| Phenytoin | Cimetidine |
| Rifampin | Ketoconazole |
| Griseofulvin | Grapefruit juice |
| Carbamazepine | Omeprazole |
| Chronic alcohol use | Chloramphenicol |
| Glucocorticoids | Marcolides |
| | Ritonavir |

FA2012 273 • FA 2011: 245.2 • FA 2010: 241.2
ME 3e: 167

# Biotransformation

**Phase I** Metabolism

- Leads to polar, water-soluble metabolites
- Non-cytochrome P450 enzyme metabolism
    - Mechanisms of metabolism:
        - Hydrolysis: Addition of $H_20$ to drugs to assist metabolism
            - Esterase
            - Amiidase
    - Monoamine oxidase: Metabolizes amines
        - Endogenous amines: Dopamine, norepinephrine, serotonin
        - Exogenous amines: Tyramine
    - Alcohol metabolism

FA 2012 260 • FA 2011: 233.4 • FA 2010: 229.4
ME 3e: 167



# Biotransformation

**Phase II** Metabolism

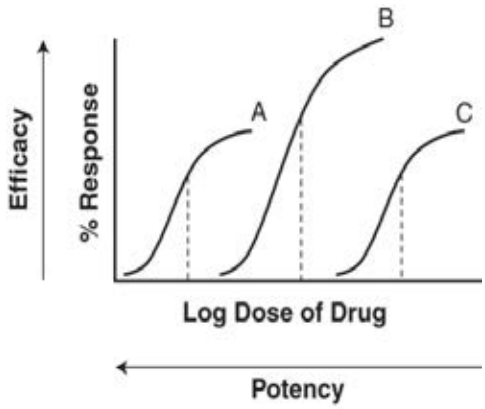
- Conjugation of functional groups to a drug
- Converts polar molecules to inactive molecules → ↑ renal excretion
- Mechanisms of metabolism:
    - Acetylation
    - Glucuronidation
    - Sulfation
    - Methylation
    - Glutathione conjugation

FA 2012 260 • FA 2011: 233.4 • FA 2010: 229.4
ME 3e: 167

# Potency vs. efficacy

**Potency:** measure of how much drug required to give desired effect
typically expressed as $EC_{50}$ - concentration that gives 50% of max. response

**Efficacy:** maximal effect that a drug can produce




B = full agonist
A = partial agonist (low efficacy) with high potency
C = partial agonist with low potency

Kaplan Pharmacology 2011: Figure I-2-2

FA 2012: 261.1 • FA 2011: 233.5 • FA 2010: 229
ME 3e: 168

x1.5 PH01- 17

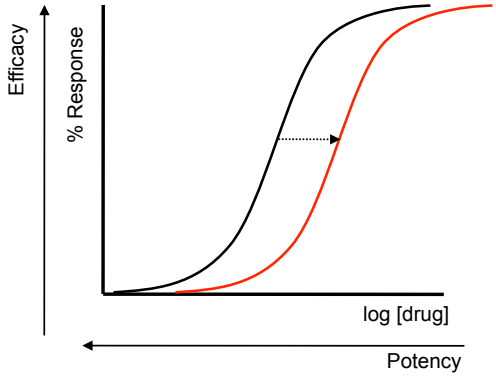
# Potency vs. efficacy

Competitive Antagonists

Potency: ↓
Efficacy: no effect

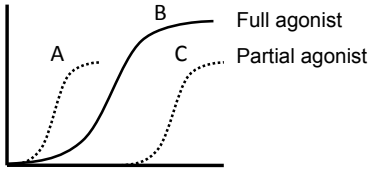
Non-competitive Antagonists

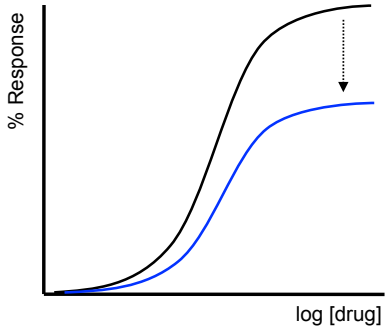
Potency: no effect
Efficacy: ↓




Partial Agonist

Acts at same site as agonist, but lower efficacy
Can have higher or lower potency than agonist



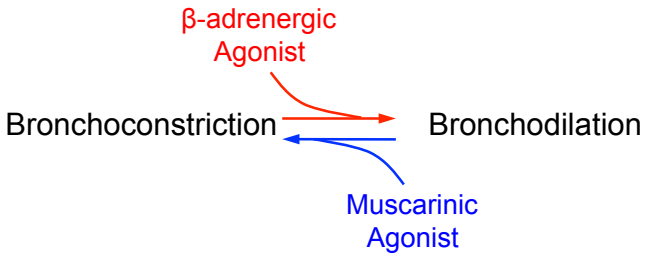

FA 2012: 261.2 • FA 2011: 234.1 • FA 2010: 230
ME 3e: 168

x1.5 PH01- 18

# Physiologic antagonists

Substrate that produces opposite effect of an agonist, but acts through different receptor/pathway

Example:



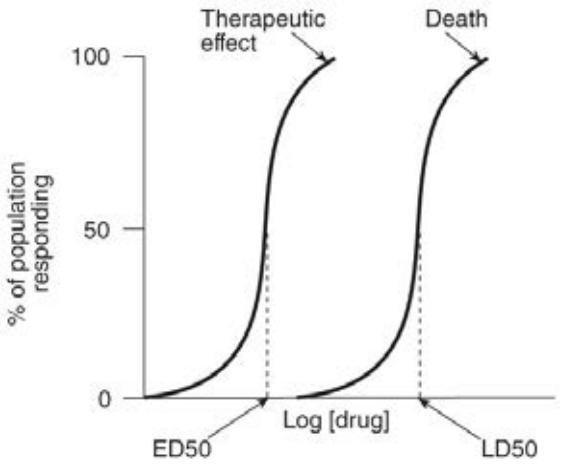

FA 2012: n/a • FA 2011: 234.2 • FA 2010: n/a
ME 3e: n/a

x1.5 PH01- 19

# Therapeutic index

Measure of drug safety. Higher therapeutic index indicates safer drug.

$$\textbf{TI} = \frac{\text{median dose that produces toxic or lethal effect}}{\text{median dose required to produce therapeutic effect}} = \frac{LD_{50}}{ED_{50}}$$




LD - lethal dose
ED - effective dose

Kaplan Pharmacology 2011: Figure I-2-5

FA 2012: 261.3 • FA 2011: 234.3 • FA 2010: 230
ME 3e: 168

x1.5 PH01- 20

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# Sympathetic and Parasympathetic Nervous Systems

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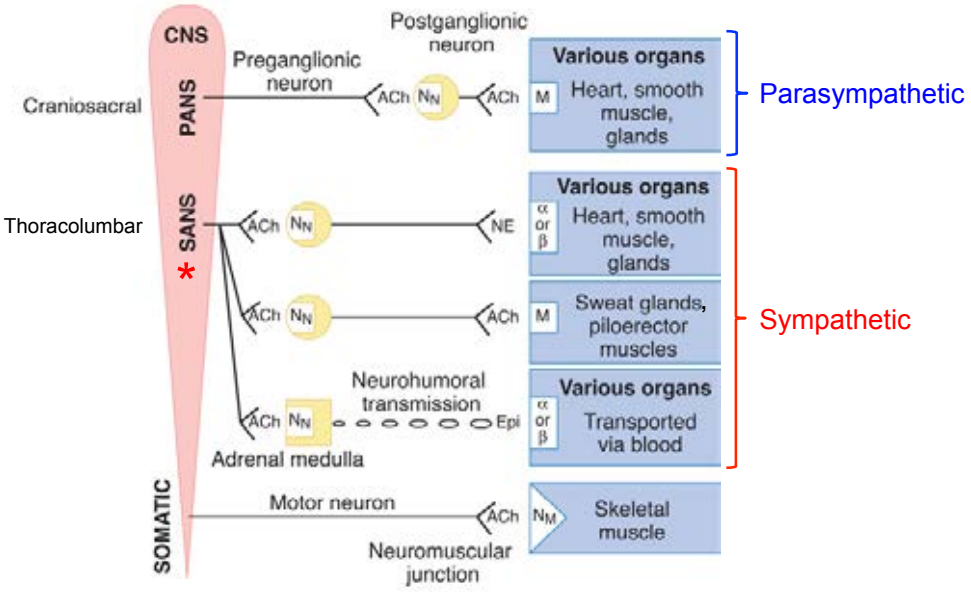
## Autonomic nervous system




* Sympathetic fibers release dopamine to activate renal vascular smooth muscle via D1 receptors

Kaplan Pharmacology 2011: Figure II-1-1

FA 2012: 262.1 • FA 2011: 235.1 • FA 2010: 231
ME 3e: 186

# Acetylcholine receptors

## Nicotinic ACh receptors (nAChRs)

Ligand-gated $Na^+/K^+$ channels

$N_N$: autonomic
$N_m$: somatic muscular (neuromuscular junction)

## Muscarinic ACh receptors (mAChRs)

G protein-coupled receptor

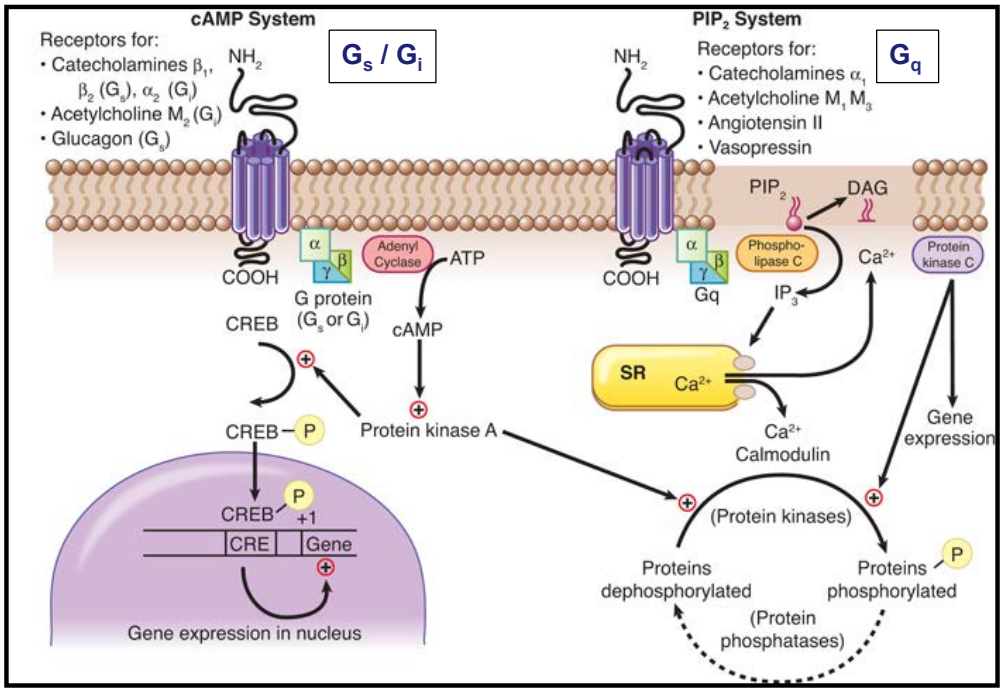
$M_1$ $M_2$ $M_3$ — Autonomic Nervous System

$M_4$ $M_5$ — CNS

FA 2012: 262.2 • FA 2011: 235.2 • FA 2010: 231
ME 3e: 189

x1.5 PH02- 3

# G protein-coupled receptor




Kaplan Pharmacology 2011: Figure I-2-6

FA 2012: 263.1 • FA 2011: 236.1 • FA 2010: 232
ME 3e: 169

x1.5 PH02- 4

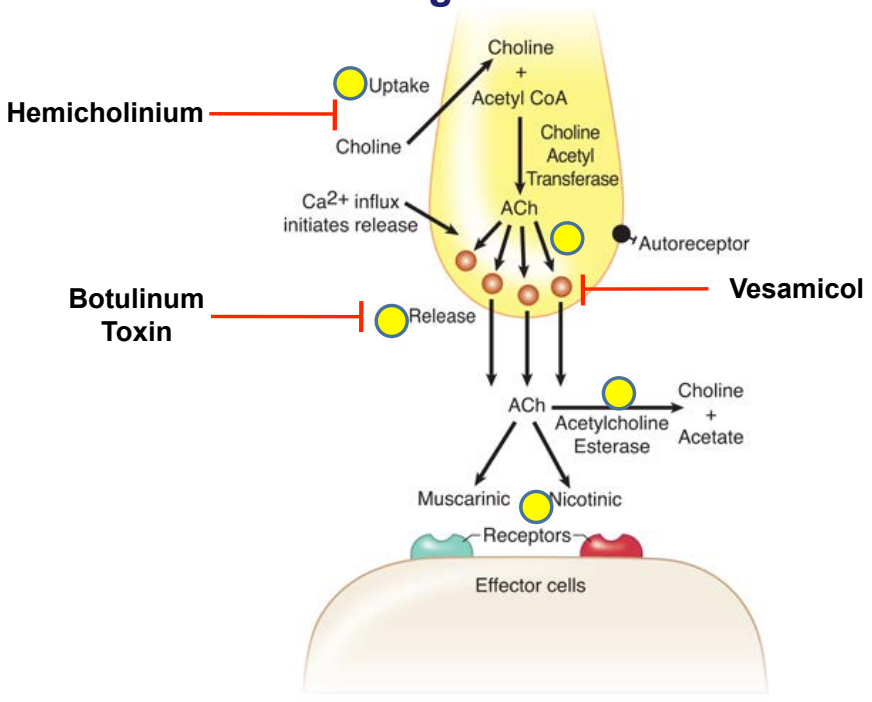
# GPCR physiology

| Class | Receptor | Functions |
|---|---|---|
| q | $\alpha_1$ | vascular smooth muscle contraction, pupillary dilation (mydriasis), intestinal and bladder sphincter contraction |
| i | $\alpha_2$ | ↓sympathetic release, ↓insulin release |
| s | $\beta_1$ | ↑heart rate and contractility, ↑renin release |
| s | $\beta_2$ | vasodilation, bronchodilation, ↓uterine tone |
| q | $M_1$ | CNS, gastric parietal cells |
| i | $M_2$ | ↓heart rate, ↓atrial contractility |
| q | $M_3$ | stimulates glandular secretions (sweat, gastric acid), ↑gut peristalsis, pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation) |
| s | $D_1$ | renal vascular smooth muscle relaxation |
| i | $D_2$ | ↓sympathetic release |
| q | $H_1$ | ↑sinus and bronchial mucus production, bronchiole constriction, itching/pain |
| s | $H_2$ | ↑gastric acid secretion |
| q | $V_1$ | vascular smooth muscle contraction |
| s | $V_2$ | ↑water reabsorption in collecting tubules of kidneys |

FA 2012: 263.1 • FA 2011: 236.1 • FA 2010: 232
ME 3e: 187

x1.5 PH02- 5

# Cholinergic nerve terminal

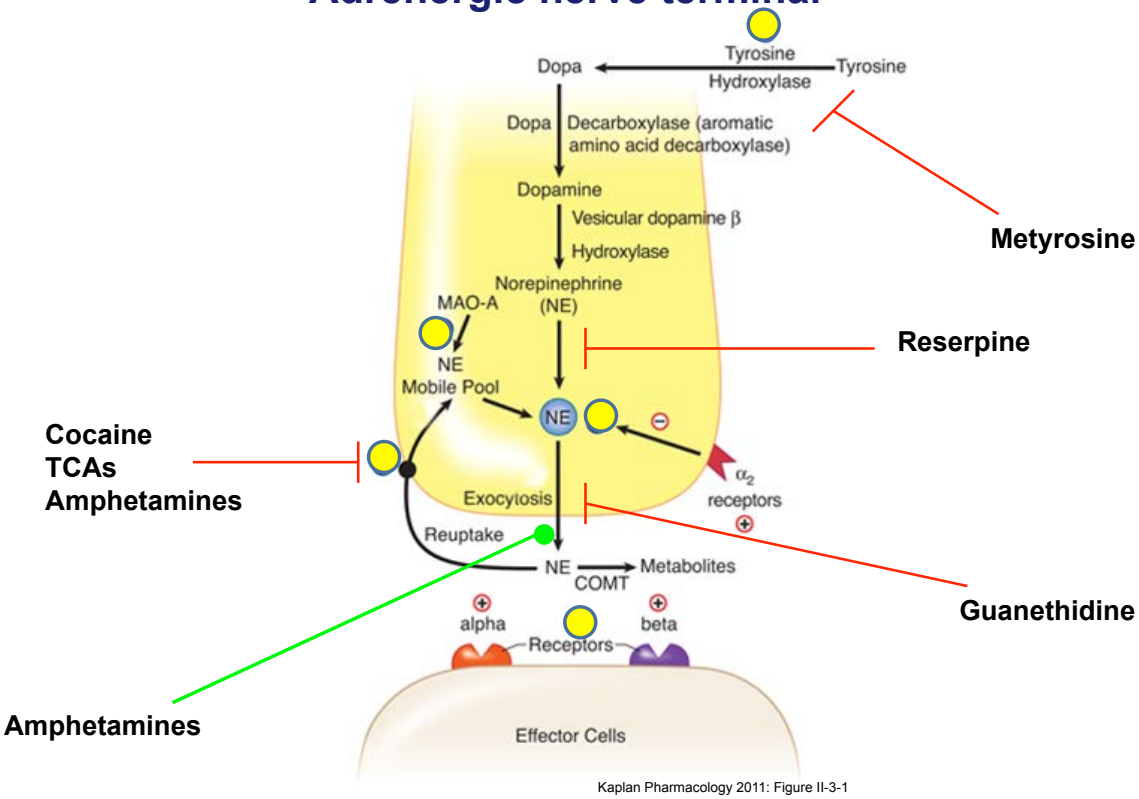



Kaplan Pharmacology 2011: Figure II-2-1

FA 2012: 264.1 • FA 2011: 237.1 • FA 2010: 233
ME 3e: 189

x1.5 PH02- 6

# Adrenergic nerve terminal




Kaplan Pharmacology 2011: Figure II-3-1

FA 2012: 264.1 • FA 2011: 237.1 • FA 2010: 233
ME 3e: 192

x1.5 PH02- 7

# Cholinomimetics

## Cholinomimetic Drugs (parasympathomimetics)

| | |
|---|---|
| **Bethanechol** | Muscarinic agonist. Longer acting than ACh (resistant to esterase). Treatment of ileus and urinary retention (**B**owels and **B**ladder) |
| **Carbachol** | Muscarinic/nicotinic agonist. Applied to eye to cause contraction of ciliary muscle, relief of open-angle glaucoma. Also constricts pupil |
| **Pilocarpine** | Muscarinic agonist. Stimulates tears, sweat, saliva. Constricts pupil and ciliary muscle. Also used for acute glaucoma |
| **Methacholine** | Muscarinic agonist. Causes bronchoconstriction when inhaled. Used for asthma challenge test |

FA 2012: 265.1 • FA 2011: 238.1 • FA 2010: 234
ME 3e: 189

x1.5 PH02- 8

# Anticholinesterases

## Anticholinesterases (indirect cholinomimetics)

| | |
|---|---|
| **Neostigmine** | Quaternary amine (no entry into CNS). Treatment of ileus, urinary retention, and myasthenia gravis. Post-operative reversal of neuromuscular junction blockade |
| **Pyridostigmine** | Quaternary amine. Treatment of myasthenia gravis |
| **Edrophonium** | Very short acting (10-20 mins.) Diagnosis of myasthenia gravis |
| **Physostigmine** | Tertiary amine (can enter CNS). Treatment of glaucoma. Antidote for atropine toxicity |
| **Echothiophate** | Treatment of glaucoma |



# Cholinesterase inhibitor poisoning

## Cholinesterase inhibitor poisoning (high systemic acetylcholine)

**Symptoms:**

**D**iarrhea
**U**rination
**M**iosis
**B**ronchoconstriction
**B**radycardia
**E**xcitation (skeletal muscle and CNS)
**L**acrimation
**S**alivation
**S**weating

**Treatment:**

Atropine (muscarinic antagonist)

Pralidoxime a.k.a 2PAM (regenerates cholinesterase)

# Muscarinic receptor antagonists

**Classic example:** Atropine

- Tertiary amine → can enter the CNS
- Effects: the opposite of DUMBBELSS

- ↓ Epithelial secretions
- Mydriasis, cycloplegia
- Hyperthermia
- Vasodilation
- Tachycardia
- Sedation
- Urinary retention
- Constipation

**Muscarinic receptor antagonists:**

| Drug | Clinical Uses and/or Characteristics |
|---|---|
| Atropine | Antispasmodic, antisecretory, management of AChE inhibitor OD, antidiarrheal, ophthalmology (but long action) |
| Tropicamide | Ophthalmology (topical) |
| Ipratropium | Asthma and COPD (inhalational)—no CNS entry, no change in mucus viscosity |
| Scopolamine | Used in motion sickness, causes sedation and short-term memory block |
| Benztropine, trihexyphenidyl | Lipid-soluble (CNS entry) used in parkinsonism and in acute extrapyramidal symptoms induced by antipsychotics |

Kaplan Pharmacology 2010: Table II-2-6



# Nicotinic antagonists

## Hexamethonium (nicotinic antagonist)

Used to prevent vagal reflexes due to sympathetic stimulation

Example: can be used to prevent reflex bradycardia caused by increased blood pressure due to increased norepinephrine

Excess hexamethonium can cause orthostatic hypotension, blurred vision, constipation

# Direct sympathomimetics

## Epinephrine:

- Function:
  - α,β agonist
  - Low doses selective for $\beta_1$ receptors
- Clinical usage:
  - Treatment for anaphylaxis, open-angle glaucoma, asthma, hypotension
  - Prolongs the effect of local anesthesia
- Adverse effects:
  - ↑systolic blood pressure + ↓diastolic blood pressure = *widened* pulse pressure

## Norepinephrine:

- Function:
  - Mainly α-receptor agonist, but has some β-receptor activity
- Clinical usage:
  - Treatment of hypotension
- Adverse effects:
  - Splanchnic vasoconstriction and ↓renal perfusion
  - ↑systolic blood pressure + ↑diastolic blood pressure = little/no change in pulse pressure
  - Reflexive decrease in heart rate



# Direct sympathomimetics

## Direct sympathomimetics

| | |
|---|---|
| **Isoproterenol** | $\beta_1$ $\beta_2$ agonist. Treatment for AV conduction block. ↓diastolic BP (this effect induces a reflexive ↑heart rate) |
| **Dopamine** | D1 = D2 > β > α agonist. Inotropic and chronotropic. Treatment for shock, especially with heart failure |
| **Dobutamine** | $\beta_1$> $\beta_2$ agonist. Inotropic. Treatment of heart failure. Used in cardiac stress test |
| **Ritodrine** | $\beta_2$ agonist. Reduces premature uterine contractions |
| **Metaproterenol**<br>**Albuterol**<br>**Salmeterol**<br>**Terbutaline** | Selective $\beta_2$ agonists ($\beta_2$>$\beta_1$). Treatment of asthma<br>Acute: metaproterenol and albuterol<br>Long-acting: salmeterol |

FA 2012: 266.3 • FA 2011: 240.1 • FA 2010: 236
ME 3e: 193

# Indirect sympathomimetics

## Indirect sympathomimetics

| | |
|---|---|
| **Amphetamine** | Induces catecholamine release from terminals. Treatment for narcolepsy, obesity, and ADHD. |
| **Ephedrine** | Induces catecholamine release. Treatment for nasal congestion, urinary incontinence, hypotension. |
| **Cocaine** | Inhibits reuptake of catecholamines. Vasoconstriction, local anesthetic. |
| **Tyramine** | Similar mechanism to amphetamines, cleared by MAO (MAO inhibitors can cause hypertension, especially with tyramine-rich foods such as wine and cheese). |

FA 2012: 267.1 • FA 2011: 240.1 • FA 2010: 236
ME 3e: 194



# Sympathoplegics

## Clonidine:

- Agonists of central $\alpha_2$-adrenergic receptors which decreases sympathetic outflow

## α-methyldopa:

- Used to treat hypertension by decreasing sympathetic tone

FA 2012: 267.2 • FA 2011: 241.1 • FA 2010: 237
ME 3e: 193

# Alpha-blockers

## Non-selective ($\alpha_1$ and $\alpha_2$)

| | |
|---|---|
| **Phenoxybenzamine** (irreversible)<br>**Phentolamine** (reversible) | Treatment of pheochromocytoma. Also used to treat Raynaud's syndrome |

## $\alpha_1$-selective

| | |
|---|---|
| **Prazosin**<br>**Terazosin**<br>**Doxazosin** (longest acting) | Treatment of hypertension, urinary retention (BPH).<br>May cause orthostatic hypotension<br>(usually taken at bedtime) |

## $\alpha_2$-selective

| | |
|---|---|
| **Mirtazapine** | Treatment of depression. Can cause sedation, increased serum cholesterol, and increased appetite |



# Beta-blockers

## Non-selective ($\beta_1$ and $\beta_2$)

Propranolol (migraines)
Timolol (glaucoma)
Nadolol
Pindolol

## $\beta_1$-selective

Metoprolol
Atenolol
Betaxolol
Esmolol (very short acting)

## Mixed α and β blockers

Carvedilol
Labetalol

## Partial β-agonists

Pindolol
Acebutolol

# Beta-blockers

## Treatments for:

- Hypertension ____ ↓CO, ↓renin production ($\beta_1$-blockade of JG cells)
- Angina ____ ↓HR, ↓inotropy, ↓myocardial $O_2$ consumption
- Myocardial infarction ____ ↓mortality
- Sinus ventricular tachycardia (SVT) ____ propranolol/esmolol to ↓AV conduction
- Heart failure (CHF) ____ slows progression of CHF (↓cardiac demand)

## Side effects:

- Exacerbation of asthma
- Impotence
- Bradycardia
- AV blockade
- Sedation
- Decreased glucagon secretion

KAPLAN MEDICAL

# Toxicology and Adverse Reaction

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## Antidotes

| Drug | Antidote |
|---|---|
| **Acetaminophen** | N-acetylcysteine |
| **Salicylates** | Sodium bicarbonate to alkalinize urine, dialysis |

FA 2012: 270.1 • FA 2011: 243.1 • FA 2010: 239
ME 3e: 172

# Antidotes

| Drug | Antidote |
|---|---|
| **Anticholinesterases Organophosphates** (insecticides) | Atropine, 2-PAM (pralidoxime) |
| **Anticholinergics** | Physostigmine |

FA 2012: 270.1 • FA 2011: 243.1 • FA 2010: 239
ME 3e: 172



# Antidotes

| Drug | Antidote |
|---|---|
| **β-blockers** | Glucagon to increase inotropy and chronotropy of heart |
| **Digitalis** | Anti-digitalis Fab fragments. Normalize serum electrolytes, especially $K^+$, then lidocaine, magnesium |

FA 2012: 270.1 • FA 2011: 243.1 • FA 2010: 239
ME 3e: 172

# Antidotes

| Drug | Antidote |
|---|---|
| **Iron** | Deferoxamine (de-Fe-roxamine) |
| **Lead** | Ca-EDTA (chelator), dimercaprol, succimer, penicillamine |
| **Arsenic, mercury, gold** | Dimercaprol, succimer |
| **Copper, arsenic, gold** | Penicillamine |

FA 2012: 270.1 • FA 2011: 243.1 • FA 2010: 239
ME 3e: 171



# Antidotes

| Drug | Antidote |
|---|---|
| **Cyanide** | Nitrite, hydroxocobalamin, thiosulfate |
| **Methemoglobin** | Methylene blue, vitamin C |
| **Carbon monoxide** | 100% $O_2$ (hyperbaric chamber) |

FA 2012: 270.1 • FA 2011: 243.1 • FA 2010: 239
ME 3e: 172

# Antidotes

| Drug | Antidote |
|---|---|
| **Methanol, ethylene glycol** | Ethanol, fomepizol |
| **Opioids** | Naloxone, naltrexone |
| **Benzodiazepines** | Flumazenil |
| **Tricyclic antidepressants** (TCAs) | $NaHCO_3$ (intravenous alkalinization), adjunctively treat for seizure, hyperthermia, and arrhythmia |

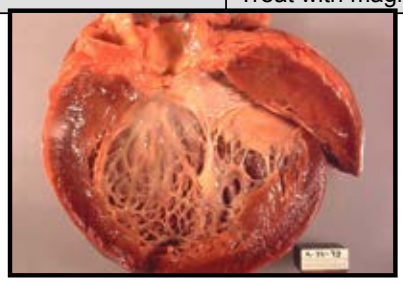


# Antidotes

| Drug | Antidote |
|---|---|
| **Heparin** | Protamine |
| **Warfarin (coumadin)** | Vitamin K, fresh frozen plasma<br>(restore factors II, VII, IX, X, and Proteins C, S) |
| **tPA, streptokinase** | Aminocaproic acid |
| **Theophylline** | β-blocker |

# Cardiovascular reactions

| Side effect | Causal agent |
|---|---|
| Atropine-like (anti-cholinergic) symptoms | TCAs, anti-histamines |
| Dilated cardiomyopathy | Doxorubicin, daunorubicin |
| Coronary vasospasm | Cocaine, sumatriptan |
| Cutaneous flushing | **V**ancomycin, **A**denosine, **N**iacin, **C**a-channel blockers (**VANC**) |
| Torsades de pointes | Class III (sotalol) and Class IA (quinidine) antiarrythmics, cisapride (update: removed from the US market because of arrhythmias) Treat with magnesium |



**Dilated cardiomyopathy**
Dr. Edwin P. Ewing, Jr., commons.wikimedia.org
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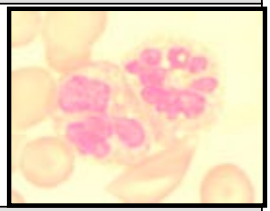
FA 2012: 271.1 • FA 2011: 244.1 • FA 2010: 240
ME 3e: 170

x1.5 PH03- 9

# Hematologic reactions

| Side effect | Causal agent |
|---|---|
| Agranulocytosis | Clozapine, carbamazepine, colchicine, propylthiouracil, dapsone, methimazole |
| Aplastic anemia | Chloramphenicol, benzene, NSAIDs, felbamate |
| Hemolytic anemia (Coombs-positive) | Methyldopa |
| Gray baby syndrome | Chloramphenicol |
| G6PD-deficient hemolytic anemia | Isoniazid (INH), sulfa drugs, aspirin, ibuprofen, nitrofurantoin, primaquin |
| Megaloblastic anemia (hypersegmented neutrophils) | Methotrexate, sulfa drugs, phenytoin |
| Thrombosis | Oral contraceptives (higher risk with smoking) |



**Hypersegmented Neutrophils**
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FA 2012: 271.1 • FA 2011: 244.1 • FA 2010: 240
ME 3e: 170

x1.5 PH03- 10

# Respiratory reactions

| Side effect | Causal agent |
|---|---|
| Cough | ACE-inhibitors (use angiotensin-receptor blockers instead) |
| Pulmonary fibrosis | Bleomycin, amiodarone, busulfan |

FA 2012: 271.1 • FA 2011: 244.1 • FA 2010: 240
ME 3e: 170



# GI reactions

| Side effect | Causal agent |
|---|---|
| Hepatitis | Isoniazid (INH) |
| Cholestatic hepatitis | Macrolide antibiotics (azithromycin, clarithromycin) |
| Hepatic necrosis | Halothane, valproic acid, acetaminophen, *Amanita phalloides* (mushroom) |
| Pseudomembranous colitis | Clindamycin, ampicillin, cephalosporins |
| Pancreatitis | Azathioprine, sulfonamides, valproic acid, methyldopa, furosemide, corticosteroids, sulindac, tetracycline, didanosine, estrogens, 6-mercaptopurine, pentamidine, 5-aminosalicyclic acid compounds, octreotide |

**Pseudomembranous colitis, endoscopy**
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ME 3e: 170

# Reproductive/endocrine reactions

| Side effect | Causal agent |
|---|---|
| Adrenocortical insufficiency | Glucocorticoid withdrawal, etomidate |
| Gynecomastia | Spironolactone, digitalis, cimetidine, alcohol, estrogens, ketoconazole |
| Hot flashes | Tamoxifen, clomiphene |
| Hypothyroidism | Lithium, amiodarone |

FA 2012: 271.1 • FA 2011: 244.1 • FA 2010: 240
ME 3e: 170



# Musculoskeletal/connective tissue reactions

| Side effect | Causal agent |
|---|---|
| Gingival hyperplasia | Phenytoin |
| Gout | Furosemide, thiazides |
| Osteoporosis | Corticosteroids, heparin |
| Photosensitivity | Sulfonamides, Amiodarone, Tetracyclines, Fluoroquinolones |
| Rash (Stevens-Johnson syndrome) | Sulfa drugs, penicillin, carbamazepine, allopurinol |
| Lupus-like syndrome | Hydralazine, INH, procainamide, phenytoin |
| Tendon rupture | Fluoroquinolones |

**Stevens-Johnson syndrome**
Dr. Thomas Habif, commons.wikimedia.org
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FA 2012: 272.1 • FA 2011: 245.1 • FA 2010: 241
ME 3e: 170

# Renal/GU reactions

| Side effect | Causal agent |
|---|---|
| Fanconi's syndrome | Expired tetracycline |
| Interstitial nephritis | Methicillin, NSAIDs |
| Hemorrhagic cystitis | Cyclophosphamide |

FA 2012: 272.1 • FA 2011: 245.1 • FA 2010: 241
ME 3e: 170



# Neurologic reactions

| Side effect | Causal agent |
|---|---|
| Cinchonism | Quinidine, quinine |
| Diabetes insipidus | Lithium, demeclocycline |
| Seizures | Bupropion, imipenem/cilastatin, INH |
| Parkinson-like syndrome | Haloperidol, chlorpromazine, reserpine, metoclopramide |
| Tardive dyskinesia | Typical antipsychotics |

FA 2012: 272.1 • FA 2011: 245.1 • FA 2010: 241
ME 3e: 170

# Multi-organ reactions

| Side effect | Causal agent |
|---|---|
| Disulfiram-like reaction | Metronidazole, procarbazine, sulfonylureas, cephalosporins |
| Nephrotoxicity / neurotoxicity | Polymxyins |
| Nephrotoxicity / ototoxicity | Aminoglycosides, vancomycin, loop diuretics, cisplatin |

FA 2012: 272.1 • FA 2011: 245.1 • FA 2010: 241
ME 3e: 170

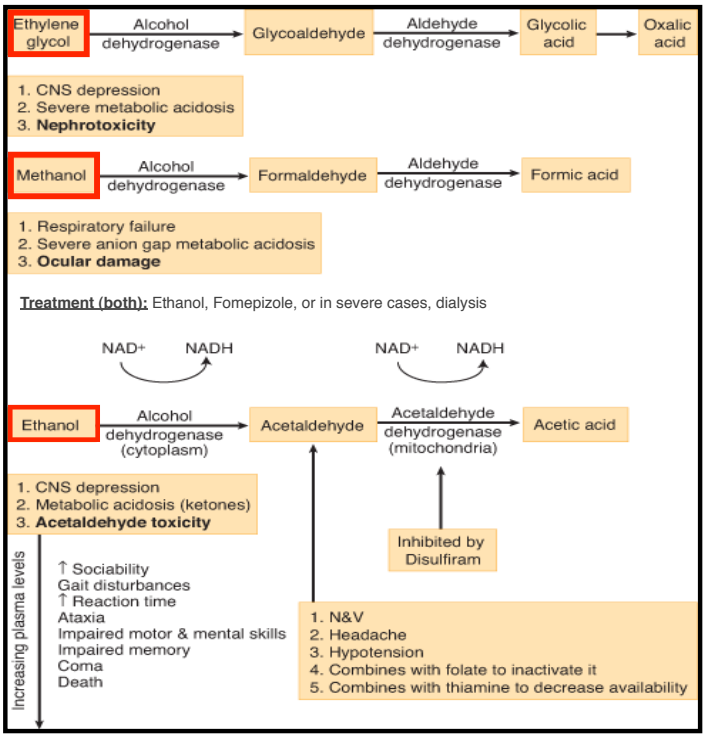


# Cytochrome P-450 interactions

| Inducers | Inhibitors |
|---|---|
| Quinidine | HIV protease inhibitors |
| Barbiturates | Isoniazid (INH) |
| St. John's wort | Sulfonamides |
| Phenytoin | Cimetidine |
| Rifampin | Ketoconazole |
| Griseofulvin | Grapefruit juice |
| Carbamazepine | Omeprazole |
| Chronic alcohol use | Chloramphenicol |
| Glucocorticoids | Marcolides |

FA 2012: 273.1 • FA 2011: 245.2 • FA 2010: 241
ME 3e: 167

# Alcohol metabolism



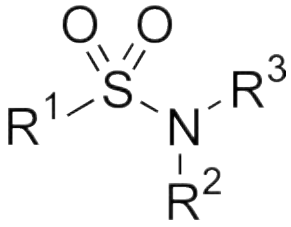

Kaplan Pharmacology 2011: Figure IV-2-1

FA 2012: n/a • FA 2011: 246.1 • FA 2010: 242
ME 3e: 13

x1.5 PH03- 19

# Sulfa drugs

- Any drugs that contain a sulfonamide group
- Allergies to these drugs are common




**Sulfonamide group**

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Drugs:
- Sulfonamide antibiotics
- TMP-SMX
- Acetazolamide
- Furosemide
- Thiazides
- Sulfasalazine
- Celecoxib
- Probenecid

Symptoms:
- Pruritic rash
- Fever
- Stevens-Johnson syndrome
- Hemolytic anemia
- Thrombocytopenia
- Agranulocytosis
- Urticaria (hives)

FA 2012: 273.2 • FA 2011: 246.2 • FA 2010: 242
ME 3e: n/a

x1.5 PH03- 20

# Common drug name endings

| | |
|---|---|
| -afil | erectile dysfunction drugs |
| -ane | inhalational anesthetics |
| **-azepam** | benzodiazepines |
| -azine | phenothiazine |
| **-azole** | antifungals |
| -barbital | barbiturates |
| **-caine** | local anesthetics |
| -cillin | penicillins |
| **-cycline** | antibiotics, protein synthesis inhibitors |
| -etine | SSRIs |
| -ipramine | tricyclic antidepressants |
| -navir | protease inhibitors |
| -olol | β antagonist |
| -operidol | butyrophenone (neuroleptic) |
| -oxin | cardiac glycoside (inotropic) |
| -phylline | methylxanthines |
| **-pril** | ACE inhibitor |
| **-terol** | $\beta_2$ agonist |
| **-tidine** | $H_2$ antagonist |
| -triptan | 5-$HT_{1B/1D}$ agonists (migraine) |
| -triptyline | TCAs |
| -tropin | pituitary hormone |
| **-sartan** | angiotensin receptor blockers |
| **-zolam** | benzodiazepine |
| **-zosin** | $\alpha_1$ antagonist |